



Research of pharmacodynamic estimation model of anti-motion sickness medicine

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ABSTRACT

Motion sickness (MS) has long been a difficult medical problem in aviation, space flight and navigation. It has become an important direction of research about how to test the efficacy of anti-motion sickness medicine (AMSM) quickly and accurately. The paper presents a fusion model by Dempster-Shafer evidence theory (DSET) for pharmacodynamic estimation of AMSM. Establishing diagnostic decision-making frame is $\Theta = \{\text{effective treatment, ineffective treatment, uncertain of treatment}\}$. The decision-making parameters are divided into the nystagmus parameters and blood microcirculation parameters according to the category. Fusion result contrasts with the Graybiel score. We found that fusion results is more obvious. It shows that fusion system has higher determination, and less subjectivity influence which is disturbed by outside factors. The mathematic model can manifest the MS symptom of the quizzee. The model can acquire important reference information for further study in the pharmacodynamic estimation of AMSM.

Key words: motion sickness; pharmacodynamic estimation; coriolis effect; Dempster-Shafer evidence theory

INTRODUCTION

Along with the continuous progress of medical instruments and medical means, the pharmacodynamic estimation method has been developing unceasingly. In recent years, the research of pharmacodynamic estimation of anti-motion sickness (PEAS) have been a significant expansion, and have made some achievements. Because of inherent complexity of MS etiology, establishment of estimation model has been a difficult problem. In 1973, the American has developed the research of military signal understanding system through the use of multi-source sensors to collect information. The system of data fusion has acquired great achievements. Multi-sensor information fusion is to combine these information data which base on certain criteria for obtaining more accurate and reliable description to the target's judgement. These information data are redundancy or complementary in space or time [1,2].

Dempster-Shafer evidence theory was put forward by Dempster in 1967 and was extended and developed by Shafer [3,4]. DSET can deal with the uncertainty which is produced as unacquaintance. It uses belief function as measurement but not probability. It set up belief function through restricting the probability of some matters, but not accounting for accurate, inestimably probability. When the restrictions turn into strict probability, DSET becomes probability theory.

The basic concept of DSET is the frame of discernment. Let Θ be the frame of discernment, i.e. the finite set of N mutually exclusive and exhaustive hypotheses, $\Theta = \{1, 2, \dots, N\}$. The power set of Θ , 2^Θ is the set the 2^N subsets of Θ , $2^\Theta = \{\Phi, 1, \dots, N, (1, 2), (1, 3), \dots, (N-1, N), (1, 2, 3), \dots, \Theta\}$, where Φ denotes the empty set.

A Basic Probability Assignment (BPA, or mass function) is a function m from 2^θ to $[0,1]$ which satisfies the following conditions: $\sum_{A \subseteq 2^\theta} m(A) = 1$, $m(\phi) = 0$. Given a BPA m , two functions from 2^θ to $[0,1]$ are defined: A belief function Bel , and a plausibility function P_l such that [5]

$$Bel(A) = \sum_{D \subseteq A} m(D), \quad \forall A \subseteq \theta \quad (1)$$

And

$$P_l(A) = \sum_{A \cap D \neq \phi} m(D) \quad (2)$$

Let m_1 and m_2 be two BPAs. The new BPA resulting from their combination is given by the Dempster's rule of combination:

$$m(A) = \frac{1}{N} \sum_{A_i \cap B_j = A} m_1(A_i) m_2(B_j) \quad (3)$$

N is called the conflict factor and is defined by $N = \sum_{A_i \cap B_j = \phi} m_1(A_i) m_2(B_j) > 0$

$m(A)$ is a measure of the belief attributed exactly to A , and to none of the subsets of A . $P_l(A)$ measures the total belief that can move into A , $Bel(A)$ measures the total belief that the object is in A . The functions m , Bel and P_l are one to one corresponding, so it's equivalent to talk about one of them, or also about the corresponding body of evidence.

2. Method

2.1. Assurance of Theory Frame and Selection of Evidence Information

Establishing diagnostic decision-making frame is $\theta = \{\text{effective treatment, ineffective treatment, uncertain of treatment}\}$. The decision-making frame is show as $\theta = \{h_1, h_2, A\}$. Each parameter of the decision-making frame θ is called as target. The targets probability of h_1, h_2, A is $m_i(h_1), m_i(h_2), m_i(A)$ respectively, where i is the number of decision-making parameters (DMP). Using fusion arithmetic calculated DMP for estimation the therapeutic effect of anti-motion sickness drugs.

We establish the targets probability with $M(\theta)$. The DMP are divided into the nystagmus parameters and blood microcirculation parameters according to the category. Nystagmus parameters include the nystagmus frequency f and the nystagmus amplitude s , blood microcirculation parameters including the change rate of oxygen saturation ΔSO_2 , the blood flow velocity v_B and the difference of blood pressure coefficient ΔP , a total of five indicators. The evidence matrix of basic probability is:

$$M(\theta) = \begin{bmatrix} m_1(h_1) & m_2(h_1) & \cdots & m_5(h_1) \\ m_1(h_2) & m_2(h_2) & \cdots & m_5(h_2) \\ m_1(A) & m_2(A) & \cdots & m_5(A) \end{bmatrix} \quad (4)$$

Where, 1 is nystagmus frequency f , 2 is nystagmus amplitude s , 3 is change rate of oxygen saturation ΔSO_2 , 4 is blood flow velocity v_B , 5 is the difference of blood pressure coefficient ΔP . After determine the DMP, we need calculate the targets probabilities of each DMP (ie, Nystagmus frequency f , the nystagmus amplitude s , change rate of oxygen saturation ΔSO_2 blood flow velocity v_B and the difference of blood pressure coefficient ΔP) inside the decision-making framework[6-8].

The each DMP in own different data section is alterable for the expression of the targets probability. Such as the ear artery blood flow, while v_B is higher than 50cm/s it is vasospasm. While v_B is less than 10cm/s it can be considered to be insufficient blood supply. So these symptoms are abnormal fluctuations. We can be directly given to the estimation probability of treatment. A subsection expression of DMP was used to calculate the evaluation about probability for the pharmacodynamic estimation.

In decision-making framework, the i -th DMP's uncertainty probability of treatment is as follows:

$$m_i(A) = \sigma_i \quad (5)$$

Where, σ_i is the i -th DMP's uncertainty probability of treatment. In the actual pharmacodynamic estimation, the DMP's σ will be evaluate ahead according to the environment and the equipment situation. i is the number of DMP. In decision-making framework, the i -th DMP's ineffective treatment probability h_2 is as follow:

$$m_i(h_2) = \frac{(e-a)P_2 - (e-b)P_1}{b-a} \quad (6)$$

Where, e is the measuring result or computing result of the DMP; P_2 is the maximum probability on the data segment; P_1 is the minimum probability on the data segment; b is the value of e when the probability is maximum on the data segment; a is the value of e when the probability is minimum on the data segment.

In decision-making framework, the i -th DMP's effective treatment probability h_1 is as follows:

$$m_i(h_1) = 1 - m_i(h_2) - m_i(A) \quad (7)$$

2.2. Fusion process of pharmacodynamic estimation model

For example, the expression of the i -th and the j -th's DMP about the probability are m_i and m_j . Pharmacodynamic estimation data fusion result of m_i and m_j is as follows:

$$m_{\Sigma_j}(h_{c+}) = \frac{m_{\Sigma_i}(h_{c+})m_j(h_{c+}) + m_{\Sigma_i}(h_{c+})m_j(A) + m_j(h_{c+})m_{\Sigma_i}(A)}{(1 - K_{\Sigma_j})} \quad (8)$$

$$\text{Where } K_{\Sigma_j} = \sum_{f \neq k} m_i(h_f) m_j(h_k) \quad f=1, 2; k=1, 2 \quad (9)$$

Fusion result's uncertainty probability is as follows:

$$m_{\Sigma_j}(A) = \frac{m_{\Sigma_i}(A) m_j(A)}{1 - K_{\Sigma_j}} \quad (10)$$

The above expression becomes the independent data. Repeating the above process we obtain last result of pharmacodynamic estimation based on evidence theory's the recursive fusion model of pharmacodynamic estimation,. After a round fusion, the system makes the estimation result.

Table 1 Targets probability estimation of DMP

parameters	σ	$m(h_2)$
f	0.1	$\begin{cases} 0\% - 90\% & a = 0, b = 5 \\ 90\% & f > 5 \end{cases}$
s	$\frac{s + 150}{1500}$	$\begin{cases} 0\% - 50\% & a = 0, b = 50 \\ 50\% - 90\% & a = 50, b = 150 \end{cases}$
ΔSO_2	$3.8 \cdot \Delta SO_2 + 0.1$	$\begin{cases} 10\% - 70\% & a = 0, b = 0.158 \\ 70\% & \Delta SO_2 > 0.158 \end{cases}$
v_B	0.15	$\begin{cases} 0\% - 70\% & a = 0.2, b = 0.1 \\ 0\% - 70\% & a = 0.2, b = 0.5 \end{cases}$
ΔP	0.15	$\begin{cases} 0\% - 85\% & a = 70, b = 40 \\ 0\% - 80\% & a = 70, b = 150 \end{cases}$

$$m(h_1) = 1 - m(h_2) - \sigma$$

In data fusion of PEAS, what needs to confirm is estimation arithmetic of the DMP to three targets (effective treatment, ineffective treatment, effect uncertain) which is in decision-making frame. At present, while we face to the problem of DMP's probability estimation, what be used to is to construct the expressions based on the discrimination rules of the DMP to decision-making frame's targets and the statistical data. According to preliminary statistical data, environment and instrument property, we evaluate ahead the relevant parameters of expression (5) and (6). Because PEAS of s and ΔSO_2 is non-linear, we use the segmented mode for evaluation, as shown in Table 1.

2.3. Experimental Method

Experimental subjects pitched the head from right to left on the rotational chair for simulation Coriolis Effect. The revolving time was 3 minutes. A total of seven groups of data were acquired and calculated for fusion. The time of acquiring the seven groups of data was respectively stationary, the first minute after the rotation, the second minute after the rotation, the third minute after the rotation, the first minute after stop rotation, the second minute after stop rotation and the third minute after stop rotation respectively. Experimental subjects were three group of healthy male(age from 25 to 30 years) without the medical history of MS .The first subject was not administered drugs. The second subject was administered anti-motion sickness.drugs. The third subject was administered placebo. The experimental process started in 30 minutes after administered medicine.

The present research found that the some DMP occur correlation and mutual following. Horizontal and vertical nystagmus frequency and amplitude contain higher correlation than other DMP. Li XC et al thought that horizontal and vertical nystagmus may acquire inconsistent experimental result because pathogenesis is different^[9]. But there is no more about the difference caused by MS in some articles. This system selects alternatively the maximal frequency and amplitude of horizontal and vertical nystagmus. The data is imported in arithmetic for fusion calculation.

RESULTS

3.1. Analyses of Fusion Results

Fusion results are estimate through ineffective treatment probability $m(h_2)$. The experiment is divided into three parts:

1)No administered medicine. Positive symptoms of MS are obvious. Fusion result is illustrated in Fig.1. Where, P_m is estimation probability of DMP. In general, MS is affected by the motion change. The appearance of MS symptoms is a course of gradual accumulation in unconformable body status. We can see that some DMP's estimation data are undulatory and fusion result of pharmacodynamic estimation is only one wave-crest from Fig. 1. The data of P_m reach the maximum value in third minute and then DMP's estimation data start to decline along with the revolving stop. Through contrasting calculational data, fusion result more obviously reflect the changes status of MS. The data of fusion show more determinately estimation result through compared to estimation probability of nystagmus and blood parameters. These results of contrast show that fusion result's estimation probability is higher than other single DMP's estimation probability when MS is in the rising cycle, and fusion result's estimation probability is lower than other single DMP's estimation probability when MS is in the decline cycle. It shows that the results of data fusion based on evidence theory are more obvious in the estimation effect than other single DMP, and have a certain forward-looking features.

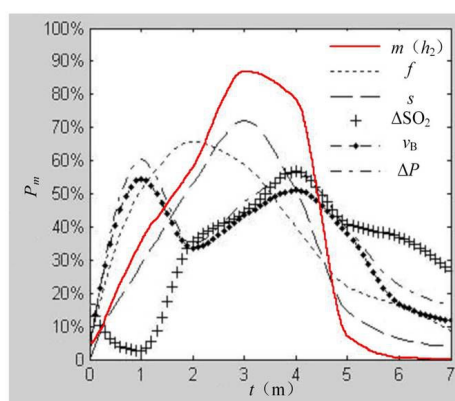


Fig.1. Estimation probability of decision parameter and fusion result during non-administered

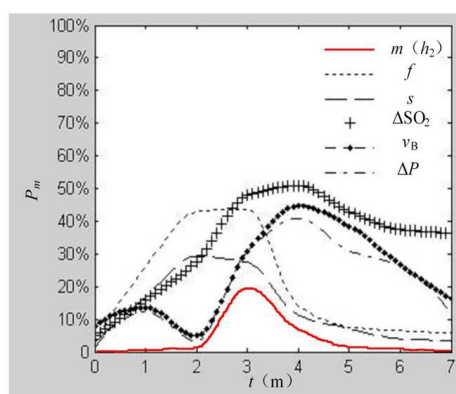


Fig.2. Estimation probability of decision parameter and fusion result after administered anti-motion sickness drugs

2) administered anti-motion sickness drugs. Slight positive symptoms of MS were found. Fusion result is shown in Fig. 2. The calculation data of nystagmus and blood parameters produced slight abnormality, but no significant difference with the normal data. Fusion result have also given the determinate estimation result that the possibility of MS was less than 20%. It showed that this medicine has obvious therapeutic effect on MS.

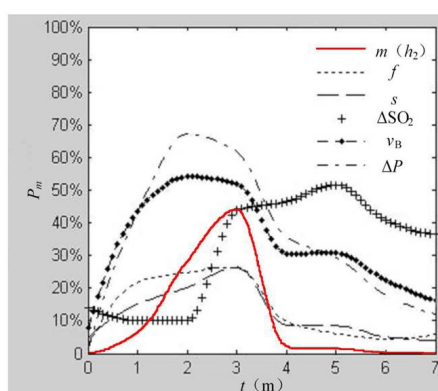


Fig.3. Estimation probability of decision parameter and fusion result after administered placebo

3) Administered the placebo. The calculation data of DMP and fusion produce a certain inconsistent result as shown in Fig.3. The result shows that the calculation data of blood parameters which are influence by autonomic nerve is inconsistent with the calculation data of nystagmus parameters which are influence by consciousness. The maximum of fusion result is about 50%. It shows the uncertainty of system to treatment result of placebo.

3.2. Comparative Analysis between Fusion result and Graybiel scoring table

Symptoms and signs of the experimental subjects were scored according to the scoring idea of MS symptom which was proposed by Graybiel [10]. The scoring criteria are established based on the normal and abnormal scope of sampling parameters, as shown in Table 2. The normal average value of every index is set as baseline, the score is 0 which express no symptom of MS. The results are converted into percentage. The contrasts between fusion results and Graybiel results are divided into three parts of no administered medicine, administered anti-motion sickness drugs and administered the placebo. We chose the beginning sampling data and just finished sampling data in the experiment for contrast because the experiment objects can't inquire and investigate in rotation, as shown in Fig.4. The estimation probability of nystagmus parameters and blood parameters use the average estimation probability in their respective DMP.

Table 2 Criteria for evaluating the symptom of MS

Category	Score				
	20	10	5	3	1
Stomach	Vomiting	Severe nausea	Mild nausea	Stomach upset	Stomach feeling
Skin	Severe pallor	Moderate pallor	Mild pallor	Flush	
Cold sweat	III	II	I		
Saliva	III	II	I		
Headache	Persistence \geq II				
Nerve system	Vertigo and close one eye \geq II				

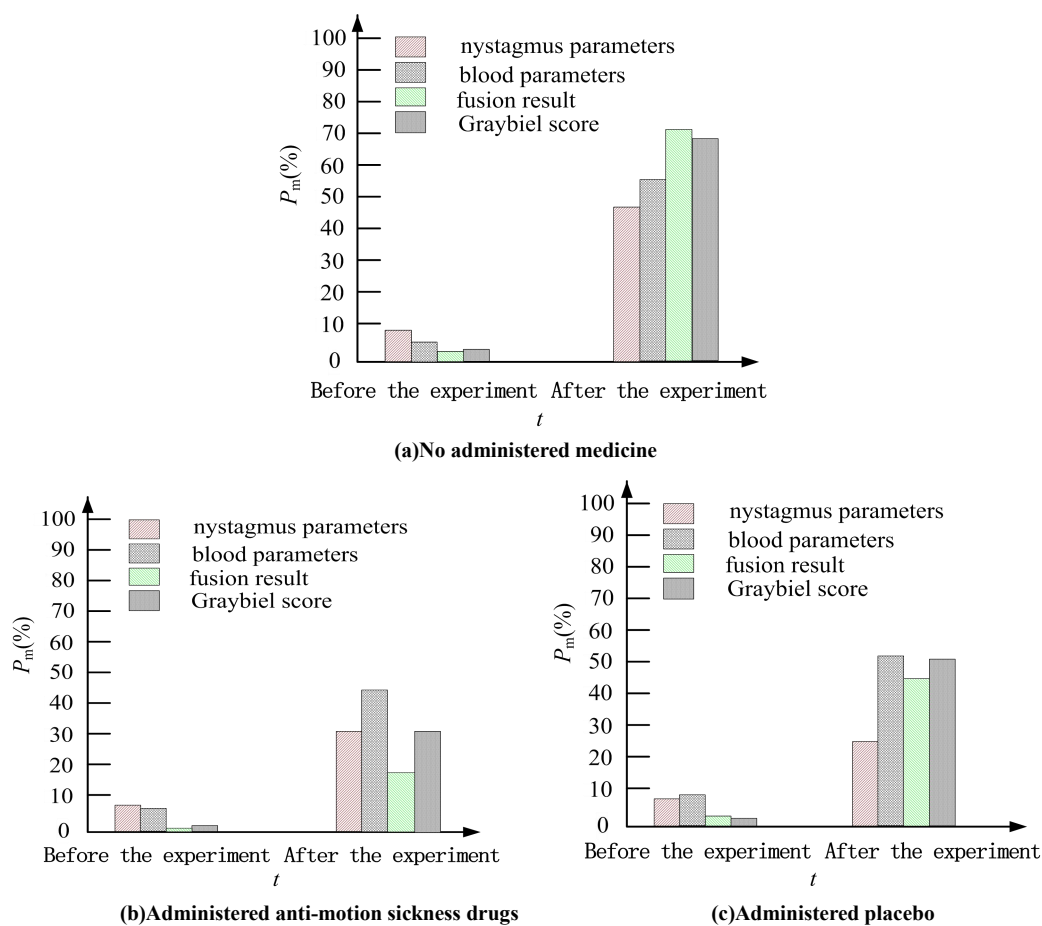


Fig.4. Correlation histogram of fusion result and Graybiel criteria

Fusion result contrasts with the Graybiel score as shown in Figure 4. Through compared between Fusion results of no administered medicine (Fig. (a)) and administered anti-motion sickness drugs (Fig. (b)) and Graybiel score, we found that fusion results is more obvious. It shows that fusion system has higher determination, and less subjectivity influence which is disturbed by outside factors. It should be indicated that fusion result of nystagmus parameters and blood parameters produced any conflict after administered the placebo (Fig. (c)). It shows that not only some symptoms of experimental object are possibly influenced by subjective factors, but also nosogenesis and treatment of MS are complicated. In summary, fusion results are approximative with Graybiel score, and can be used for the research of PEAS.

DISCUSSION

Data fusion is an estimation way through imitating the human idea. It resolves uncertain estimation of single information and conflict of multi-information. Compared with Fig. 1, Fig. 2, Figure 3 and Figure 4, fusion results present three characteristics:

- 1) Fusion results are less affected by interference. When single estimation is in the rising cycle or the decline cycle, its data would sometimes present certain fluctuation. But fusion result always keeps steady rising or decline. It is less affected by fluctuated DMP.
- 2) When experimental object took the placebo, fusion result is closely 50%. It indicated that therapeutic effect is unsure. This estimation is a reasonable result.
- 3) The rapid decline of fusion estimation is inconsistent with the slow disappearance of positive symptoms of MS. The phenomena illuminate that the process of fusion estimation is sensitive to decline of estimation of DMP. Especially, when a group of DMP's estimation still slow decline, but another group of DMP's estimation rapid decline, the fusion process is easily influenced to decline in advance.

Analyzing the data of DMP and fusion result, we can find that estimation method of using the D-S evidence theory still need two improvement: Firstly, the DMP should increase independent and reduce interrelated, such as blood flow velocity and vascular pressure difference, nystagmus frequency and amplitude are interrelated to a certain

extent. But some interrelations are inevitable. Secondly, the estimation probabilities of fusion result rapidly change in the end of the experiment. Solving these two problems need analyze a large number of experimental data and compare therapeutic effect. Some degree of interrelations need be found in the sampled data. Based on the degree of interrelations, DMP would be dynamically weighed. Sensitivity of fusion results would be reduced so that it can correctly show therapeutic effect of anti-motion sickness drugs.

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